Activity 4
Are You Susceptible?

Focus: Students play a game to explore the relationship between genetic variation and environmental factors in the onset of heart disease and consider the implications for disease prevention of increased knowledge about genetic variation.

Major Concepts: Studying the genetic and environmental factors involved in multifactorial diseases will lead to increased diagnosis, prevention, and treatment of disease.

Objectives: After completing this activity, students will

- understand that all disease, except perhaps trauma, has both a genetic and environmental component;
- recognize that certain behaviors can increase or reduce a person's risk of experiencing certain medical outcomes; and
- understand that the ability to detect genes associated with common diseases increases the prospects for prevention.

Prerequisite Knowledge: Students should understand the concept of a gene.

Basic Science-Health Connection: The last few years of research have seen a gradual transition from a focus on genes associated with single-gene disorders to an increasing focus on genes associated with multifactorial diseases such as cancer, heart disease, and diabetes. In this activity, students investigate the contribution that genes associated with heart disease might make to its development in an individual's life and consider the implications of this knowledge for behavior.

Activity 3, *Molecular Medicine Comes of Age*, and Activity 4, *Are You Susceptible?*, focus students' attention on the practical, medical applications of understanding human genetic variation at a molecular level. Activity 3 looks at treatment options that become possible with the discovery and sequencing of a disease-related gene. In contrast, Activity 4 focuses on the likelihood that genetic testing for common, multifactorial diseases will increase in the future and invites students to consider the prospects for this information to help individuals make wise decisions about their personal health. Specifically, Activity 4 uses heart disease as an example of the common, multifactorial diseases that constitute the bulk of the health care burden in the United States and other developed countries. The activity builds on the treatment of variation in the prior activities and sets up the discussion of ethics that is central to Activity 5, which deals with genetics and cancer.

For the most part, the treatment of genetics in the high school curriculum focuses on single-gene traits. In addition, most of the single-gene traits discussed in the curriculum are disorders, because they provide reasonably

straightforward examples of Mendelian patterns of inheritance. Research in human genetics, however, increasingly addresses multifactorial traits, that is, traits that result from the interaction of multiple genes and environmental factors. Among the multifactorial traits that come most quickly to mind are those behavioral characteristics that are controversial and that often attract media attention, for example, intelligence, sexual preference, aggression, or basic personality traits such as novelty-seeking behavior or shyness. Research into the relative genetic and environmental contributions to behavioral traits has been uneven and is confounded by the difficulty of defining and measuring the phenotypes in question with any degree of accuracy and reliability.

A more productive area of active investigation involves the multifactorial diseases that are among the leading causes of sickness and death in developed countries, for example, heart disease, cancer, diabetes, and even psychiatric disorders such as schizophrenia and bipolar disease (manic-depressive illness). Already, research has uncovered genetic markers, and in some cases specific genes, that are associated with the development of these maladies; more genetic associations are sure to emerge as research into human genetic variation expands.

The identification of more genetic associations raises the virtual certainty of genetic testing for common, multifactorial diseases. Genetic testing is not a new phenomenon; it is done routinely to determine the risk for or presence of a number of single-gene disorders, including examples of Mendelian inheritance in the high school curriculum: Tay-Sachs disease, cystic fibrosis (CF), Huntington disease, phenylketonuria (PKU), and Duchenne muscular dystrophy. The predictive power of these tests lies in their technical reliability and the direct connection between gene and phenotype. Although there is considerable variation in symptomology for many single-gene disorders, the presence of the gene (or genes) does result in the generally recognized phenotype.

Our knowledge of the biological relationship between gene and phenotype is much less certain for multifactorial diseases. It is clear, for example, that genetic factors contribute to the risk for early onset heart disease, but the exact relationship is as yet unclear, as is the case for the relationship between certain genetic markers and the risk of schizophrenia. In these cases, the distance between gene—or genes—and phenotype is greater than it is in single-gene disorders, likely because of a host of environmental variables whose influences on phenotype are difficult to discern.

Genetic testing for common, multifactorial diseases will affect more people than does testing for relatively rare, single-gene disorders. Many of the same ethical and policy questions will apply—privacy and confidentiality, for example—but the uncertainty inherent in genetic testing for multifactorial

disease will introduce some new challenges for the public, chief among them the notions of susceptibility and risk. One may learn from a "positive" test that one is susceptible to developing the disease in question, but that will not mean that one is destined to develop the disease. Nor will a "negative" test mean that one definitely will not develop the disease. In addition, while one may learn that there is an increased *relative* risk of developing a given disease—that is, a risk that is increased above the risk for the general population—the *absolute* risk may still be quite low.

It is likely that a deeper understanding of both the molecular basis of common, multifactorial diseases and the advent of genetic testing for these diseases will improve the climate for the development of more focused clinical interventions and for preventive medicine. Multifactorial diseases tend to develop later in life than do single-gene disorders, which generally exact their toll in infancy, childhood, or adolescence. There is, therefore, more opportunity to ameliorate the effects of multifactorial disease through a combination of medication and environmental modification. That, of course, requires a partnership between patients and health care providers to identify and modify the environmental variables that magnify one's genetic risks. That is the ultimate message of this activity.

Materials and Preparation

You will need to prepare the following materials before conducting this activity:

- Master 4.1, *Rolling the Dice* (make 1 copy per student)
- Master 4.2, *Thinking About the Game* (make 1 copy per student)
- dice (1 die per student)
- relevant genes envelopes (make 1 envelope per student)

To make a classroom set of relevant genes envelopes, first make as many copies of Masters 4.3–4.6 as you need to provide one-fourth of your class with the genetic risk indicated on each master. To minimize copying, each master contains four of the same statements. Insert one statement into each envelope and label the envelope "Relevant Genes."

Procedure

1. **Begin the activity by asking students to suggest definitions of the term "risk." You might prompt the discussion by asking the students to think about risky behaviors that are a part of adolescence. Write three or four of their definitions on the board.**

    Students may suggest that "risk" refers to the chance that something bad or negative will happen, as, for example, "the risk" involved with dangerous behaviors. Help students see that one way to think about risk is in terms of one's chance of experiencing a particular event. For example, if a person performs aerial acrobatics on skis, he or she has some "risk" of getting hurt.

2. **Ask students whether they think risks can be modified. For example, ask them if there is any way they can modify their risk of being robbed or their risk of heart attack or cancer.**

   Answers will vary.

3. **Read the following story to the students:**

   ### Death of an Olympic Champion*
   Ekaterina Gordeeva and Sergei Grinkov, young Russian figure skaters, had won two Olympic gold medals in the pairs competition and were expected to continue dazzling audiences and judges for years into the future. In November 1995, however, 28-year-old Sergei suddenly collapsed and died during a practice session. He was a nonsmoker, he was physically fit, and there had been no warning signs. What happened to cause this young athlete's early death?

   *Source: Courtesy of Sinauer Associates, Inc., from Mange and Mange: *Basic human genetics*, Second Edition, 1999.

4. **Explain that Sergei Grinkov was born with a mutation [called *PL(A2)*] in a single gene that affects the formation of blood clots. The mutation causes clots to form in the wrong places at the wrong time. If such a clot forms in one of the arteries that supplies the heart, a heart attack can result. Ask the students to consider whether this mutant allele influenced Sergei Grinkov's risk of a premature heart attack.**

   The mutant allele increased Grinkov's risk of premature heart attack *relative* to the risk for the general population. Relative risk is the risk for any given person (or group) when considered in relation to the rest of the population. One may have an elevated relative risk, but still have a low *absolute* risk. For example, one may have an increased risk of 20 percent above the risk for the general population, but may still only have a 5 percent risk of suffering the disease in question by, say, age 50.

5. **Ask the class to suggest ways that Sergei Grinkov could have modified his behavior had he known he was at increased risk for premature heart attack.**

   Given that this single-gene disorder affects the clotting process, it likely would have been difficult to reduce the risk of heart attack by modifying the environment. There is some indication that the PL*(A2)* mutation can interact negatively with increased cholesterol levels. If, for example, plaques formed by excess cholesterol break off from the lining of a coronary artery and create a lesion in a blood vessel, the *PL(A2)* mutation can cause the formation of a clot that impedes blood flow, resulting in a heart attack. Maintaining low cholesterol levels through diet and exercise, therefore, might reduce the risk of premature heart attack for a person who carries the *PL(A2)* mutation.

6. **Explain to the students that premature heart attacks resulting from single-gene disorders are uncommon. Most heart attacks occur later in life and result from a combination of genetic and environmental factors that produce atherosclerosis, the build-up of cholesterol deposits in the arteries. In this activity, students will have an opportunity to explore the idea of medical risk and learn how genetic analysis is helping us understand and define people's risks in new ways.**

7. **Distribute one copy of Master 4.1, *Rolling the Dice*, to each student and direct the students to work in teams of three to play the game described.**

   Give the students about 10 minutes to finish the game.

8. **Ask how many students suffered a fatal heart attack. Determine at which life stages the heart attacks occurred and record this information on the board.**

9. **Ask the students how the game is and is not like real life.**

   The game is like real life in that life expectancy depends on many risk factors. The game is not like real life because students rolled the die to determine what their risk factors would be instead of making personal choices. The game also involved only environmental risk factors, not genetic factors. If students fail to mention that the game does not address genetic risk factors, try to elicit that response by asking about Sergei Grinkov.

10. **Acknowledge the importance of considering genetic risk factors in the development of heart disease and ask students what effect(s) factoring this information into the game might have.**

    Answers will vary. Because of the example of Sergei Grinkov and because of their own sense that sometimes heart disease tends to "run in families," students may think that including genetic factors in the game will inevitably have a negative effect. You may choose to point out that for some people, the effect might be positive, or let students discover this in Step 11.

11. **Distribute one relevant genes envelope to each student and explain that this envelope contains information about his or her genetic risk for a fatal heart attack. Ask the students to open the envelopes and share their heart points until you have addressed all four values: -10, 0, +10, +40. Point out that the genetic risk falls off rapidly as genetic relatedness decreases, from 40 points for first-degree relatives to no points for third-degree relatives. Explain that this is the case generally for multifactorial diseases.**

12. **Distribute one copy of Master 4.2, *Thinking About the Game*, to each student and ask students to complete the worksheet to compare the results of the game with and without considering genetic factors.**

This part of the game is futuristic, in that at this time, we either do not have the technology available to determine each person's individual risk, or, if this technology is available, conducting such genetic testing is not yet a regular part of medical care. Nevertheless, you may wish to point out to students that with the rapid pace of our progress in understanding the molecular basis for disease, such testing may well be in their future.

You may wish to collect your students' answers to these questions to evaluate how well they understand the issues involved.

13. **Conclude the activity by inviting each team to offer its answer to one of the questions on Thinking *About the Game*. Then, invite other teams to contribute additional insights or information or to challenge ideas expressed by the team answering.**

Question 3 Remember, if you exceeded 85 points in any life stage, you have had a fatal heart attack. What effect did including your points for genetic risk have on your outcome?

Answers will vary. Including the genetic data may have pushed some students over the threshold to a heart attack. Others may have escaped a heart attack because of the protective effects of their genes, while still others may have experienced no change. The important point is that the environmental risks—the choices they made—have been played out against a genetic background, which differs for each person.

Question 4 Think about the choices you made in each life stage.

a. Did everyone make the same choices?

No, each person made somewhat different choices.

b. Were all of the choices equally risky?

No, some of the choices carried greater risks than others, and some decreased the risks.

c. Were the risk factors associated with the choices reversible?

Most of the risk factors were reversible—smoking, exercise, and stress, for example.

d. Were the choices under personal control?

In the game, choices were made on the basis of a roll of a die. In life, however, most of these choices are under personal control.

Question 5 Now, think about the effects of genetic risk factors in each life stage.

a. Does everyone have the same genes?

No, each person (except identical twins) has different genes.

b. Did all of the genetic factors have the same effect?

No, some genetic factors had negative effects, some were neutral, and some provided protection.

c. Were the genetic factors reversible or under personal control?

We cannot change the genes with which we are born. We can, however, sometimes modify the *effects* of those genes by modifying the environment, for example, by changing some of our behaviors.

Question 6 Assume that genetic testing showed that you were at increased risk for a fatal heart attack 20 years from now. Would you want to know? Why or why not? Would that information cause you to change your behavior? If not, what kind of information or event would cause you to change your behavior?

Answers will vary, but the assumption is that knowledge of increased genetic risk would cause one to modify his or her behavior to reduce the environmental risk factors. A very important point here is that a family history of heart disease is an indication of increased genetic risk, even if we are not yet able to identify predisposing genes and attach some risk figure to them. The literature on health and behavior—and personal experience—demonstrates that people do not always change their behaviors in the face of well-documented risk. Cigarette smoking is perhaps the classic example that applies well to adolescents. Some people will not change their behavior even in the face of serious illness.

Question 7 We know about only a few genes that affect the likelihood of a heart attack, and we have the ability to test for even fewer of them. In the future, we certainly will learn about more of these genes. How will an increased knowledge of the genetic factors associated with heart disease have a positive impact on individuals and society? How will it have a negative impact?

Increased knowledge about such genes will lead to increased testing and the development of new clinical interventions. Our ability to test for genes that predispose to heart disease will mean that we can detect those genetic susceptibilities sooner and act on them more quickly, for example, with drugs targeted at the specific biochemical defects involved and with modification of risky behaviors.

The frequency of heart disease, and other common, multifactorial diseases, means that genetic testing will be applied to many more individuals, with attendant concerns about how we use the results of genetic testing. In addition, genetic testing for multifactorial diseases will require education of the public and health care providers about the meaning of susceptibility and predisposition. Activity 5 explores some of these issues in more detail.

Question 8 Our ability to detect genetic variations that are related to common diseases will improve. How might that ability shift some of the responsibility for health care from physicians to individuals?

If we know that we are at increased genetic risk for a particular disease, we can try to avoid those environmental factors, such as risky behaviors, that increase the risk further. Many health care professionals think that increased understanding of genetic variation will provide an important impetus to preventive medicine. Prevention will

This question is designed to draw students' attention back to the activity's major concept.

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require a close partnership between health care providers and consumers. Health care specialists may be able to provide us with tests to uncover our genetic predispositions, but it will be up to each one of us to avoid increasing those risks by engaging in high-risk behaviors. In short, each of us will have to assume more responsibility for our own health. This requires active participation by the individual and is very different from the prevailing model, which is based not on prevention but on treatment after the disease occurs. In the current model, the individual (the patient) generally is a rather passive recipient of health care.